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(21) International Application Number: PCT/US93/09585 (22) International Filing Date: 6 October 1993 (06.10.93) (30) Priority data: 957,231 6 October 1992 (06.10.92) US (60) Parent Application or Grant (63) Related by Continuation US 957,231 (CIP) Filed on 6 October 1992 (06.10.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	(72) Inventors; and (75) Inventors/Applicants (for US only) : RASMUSSEN, Gary, H. [US/US]; 155 Park Place, Watchung, NJ 07060 (US). BAKSHI, Raman, K. [IN/US]; 9 Azalea Drive, Edison, NJ 08820 (US). PATEL, Gool, F. [US/US]; 60 Nottingham Way, Millington, NJ 07946 (US). (74) Agent: QUAGLIATO, Carol, S.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims.</i> 7	
(54) Title: 17 β -CARBOXANILIDES OF 4-AZA-5 α -ANDROSTAN-3-ONES AS 5 α -REDUCTASE INHIBITORS (57) Abstract Described are new 17 β -carboxanilides of 4-aza-5 α -androstan-3-ones and related compounds and the use of such compounds as 5 α -reductase inhibitors for treatment of benign prostatic hyperplasia and other hyperandrogenetic related disorders.		

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TITLE OF THE INVENTION**17 β -carboxanilides of 4-aza-5 α -androstan-3-ones as 5 α -reductase inhibitors**

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BACKGROUND OF THE INVENTION

The present invention is directed to new 17 β -carboxanilides of 4-aza-5 α -androstan-3-ones and related compounds and the use of such compounds as 5 α -reductase inhibitors.

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DESCRIPTION OF THE PRIOR ART

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hyperplasia, are the result of hyperandrogenetic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, compete with all natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host and/or initiate feed-back effects which would cause hyperstimulation of the testes.

20

It is now known in the art that the principal mediator of androgenic activity in some target organs, e.g. the prostate, is 5 α -dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5 α -reductase. It is also known that inhibitors of testosterone-5 α -reductase will serve to prevent or lessen symptoms of hyperandrogenetic stimulation.

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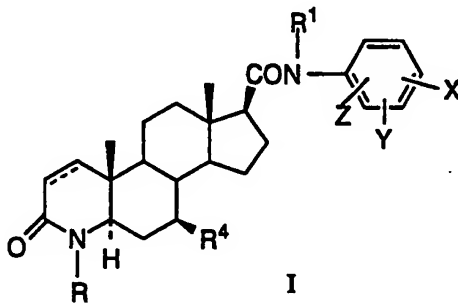
For example, a number of 4-aza steroid compounds are known which are 5α -reductase inhibitors. See the following Merck & Co., Inc. patents, U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., and U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al., and EP Publication No. 0 484 094 to Sankyo, which describe 4-aza-17 β -substituted- 5α -androstan-3-ones said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, none of the above references specifically describe the compounds of the instant invention, which are selective and potent inhibitors of 5α -reductase in humans, as well as animals, i.e. dogs, which are exceptionally active.

SUMMARY OF THE INVENTION

The present invention discloses novel anilide derivatives of 17 β -carboxy-4-aza- 5α -androstan-3-ones which are useful for inhibiting the 5α -reductase enzyme in prostatic tissue and isozymes thereof. They are also particularly effective in selectively inhibiting mammalian 5α -reductase for the treatment of benign prostatic hyperplasia in humans and dogs, acne, female hirsutism, androgenic alopecia, i.e., male pattern baldness and treatment of prostatic carcinoma.

In accordance with the present invention there is provided novel anilides of 17 β -carboxy-4-aza- 5α -androstan-3-one and related compounds of the formula:



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wherein:

R is H, CH₃, or C₂H₅;

R¹ is H, C₁-C₁₀ alkyl, or phenyl; and

5 X, Y and Z independently represent -H; -OH; -NH₂; SH; -SC₁-C₄alkyl;
-CO₂H; -CN; -C₂-C₁₀ acyl; -C₇-C₁₅ aroyl; straight or branched chain
alkyl having 3, 4, 5, 6, 7, or 8 carbon atoms; -C₃-C₈ cycloalkyl; -C₆-
C₁₄ aryl; heteroaryl; heteroaroyl; -C₇-C₁₀ aralkyl; -CONR²R³ where
10 R² and R³ independently are H, C₁-8 alkyl, C₃-8 cycloalkyl, C₆-C₁₄
aryl, or R² and R³ together with the nitrogen to which they are attached
form a 5-7 membered saturated heterocyclic ring containing 1-2
nitrogen atoms, and 0-1 oxygen atoms;

-NHCOR²;

-OCOR²;

15 -NR²(CO)R³;

-NR²(CO)NHR³;

-NH₂SO₂R²;

-OR²;

-NR²R³;

-CO₂R²;

20 provided that X, Y, and Z cannot simultaneously be -H when R¹ is -H
or C₁-10 alkyl, and provided further that X, Y, and Z cannot
simultaneously be -H when R¹ is phenyl and R⁴ is -H or methyl;
and

25 wherein the aryl, aroyl, heteroaryl, and heteroaroyl substituents can be
unsubstituted or substituted by 1-3 substituents as defined above for X,
Y and Z;

R⁴ can be: 1) oxo;

2) alpha-hydrogen and beta-hydrogen or a beta-
30 substituent selected from: C₁-C₄ alkyl; C₂-C₄ alkenyl;
-CH₂COOH; hydroxy; carboxy; -COOC₁-C₄ alkyl
esters; -OCONR⁵R⁶, wherein R⁵ and R⁶ are independently H, C₁-C₄
alkyl, phenyl, benzyl, or R⁵ and R⁶ together with the nitrogen to which

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they are attached can form a 5-6 membered saturated heterocyclic ring, optionally containing one other heteroatom; -OC₁-C₄ alkyl; -OC₃-C₆ cycloalkyl; -OCOCH₃; halo; hydroxy C₁-C₂ alkyl; halo C₁-C₂ alkyl; trifluoromethyl; and C₃-C₆ cycloalkyl;

- 5 3) =CH-R' where R' is H, or C₁-C₄ alkyl;
 4) spiro:



- 10 where R' is H, or C₁-C₄ alkyl;
 and wherein the dashed line can represent a double bond when present;
 and pharmaceutically acceptable salts and esters thereof.

- Also disclosed are processes for their preparation,
 pharmaceutical formulations comprising the novel compounds
15 as active ingredients and methods of inhibiting 5 α -reductase in diseases
 which occur under hyperandrogenetic conditions, e.g., benign prostatic
 hyperplasia.

20 DETAILED DESCRIPTION OF THE
 INVENTION AND PREFERRED EMBODIMENTS

 The structure I above encompasses all the 5 α -reductase inhibitor compounds of this invention.

 The dashed line can independently be a double bond and, when present, the compound is a delta-1-ene.

- 25 The aryl ring of the anilide can be unsubstituted or
 substituted with one or more of the following substituents indicated by X, Y and Z, providing the substitution leads to a chemically stable, but biologically active 5 α -reductase inhibitor.

- By the term "C₁-C₄ alkyl" is meant linear or branched
30 alkyl ; e.g. methyl, ethyl, isopropyl, propyl, n-butyl, isobutyl, sec-butyl
 and the like.

 By the term "hydroxy C₁-C₂ alkyl" is meant monohydroxy C₁-C₂ alkyl including: hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, and the like.

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By the term "halo C₁-C₂ alkyl" is meant mono halogenated C₁-C₂ alkyl including: fluoromethyl, chloromethyl, 1-fluoroethyl, 2-fluoroethyl, 1-chloroethyl, 2-chloroethyl, and the like.

By the term "OC₁-C₄ alkyl" as used herein is meant to
5 include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy, and the like.

By the term "OC₃-C₆ cycloalkyl" as used herein is meant to include: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

10 C₂-C₄ alkenyl includes ethenyl, allyl, 1- and 2-butenyl and the like.

C₃-C₆ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Halo" includes fluoro, chloro, bromo and preferred is
15 fluoro, chloro.

R⁵ and R⁶ can also be connected to form a 5-6 membered heterocyclic radical, being fully saturated, containing 1-2 nitrogen atoms and 0-1 oxygen atoms, e.g., piperidino, pyrrolidino, morpholino, and the like.

20 The phenyl and benzyl groups in R⁵ and R⁶ can be unsubstituted or substituted with one or more of the following substituents providing the substitution leads to a chemically stable, but biologically active 5- α reductase inhibitor:

The ring substituents include:

25 C₁-C₄ straight or branched alkyl;

C₁-C₅ alkoxy; and

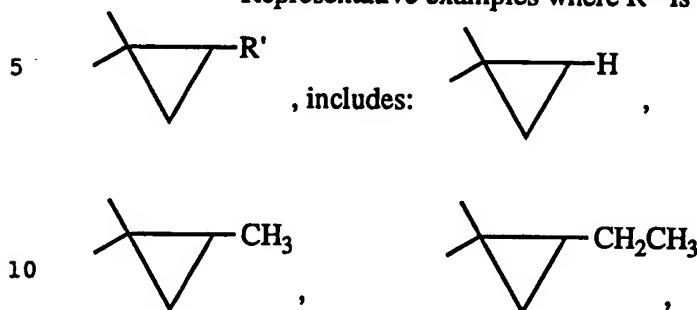
halo; all as defined above.

Representative examples of R⁴ are where the α -substituent (dashed lines) is hydrogen and the beta substituent (wedge) is e.g.
30 methyl, ethyl, propyl, allyl, carboxymethyl, hydroxy, methoxy, ethoxy, cyclopropyloxy, cyclopentyloxy, acetoxy, fluoro, chloro, bromo, trifluoromethyl, trichloromethyl, fluoromethyl, chloromethyl, carboxy, N,N-dimethylcarbamate, hydroxymethyl, methoxymethyl, and the like.

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Representative examples where R^4 is an alkenyl substituent, $=CH-R'$, includes, e.g. $=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$, and the like.

Representative examples where R^4 is the spiro substituent:



stereoisomers thereof and the like.

By the term "C₁-C₁₀ alkyl" is meant linear or branched alkyl hydrocarbon; e.g. methyl, ethyl, isopropyl, propyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, iso-hexyl, n-octyl, iso-octyl, t-octyl, n-decyl, and the like.

By the term "C₁-C₈ alkyl" is meant a saturated straight or branched chain hydrocarbon radical containing 1-8 carbons including those described above.

By the term "C₃-C₈ cycloalkyl" is meant e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclobutyl, cyclopentyl, cyclohexyl, 1-methyl-cyclohexyl, 2-methylcyclohexyl, 2-ethylcyclohexyl, and the like;

By the term "C₂-C₁₀ acyl" is meant C₁-C₉ alkyl-carbonyl, including acetyl, n-propionyl, iso-butyryl, n-decanoyl, and the like.

By the term "C₇-C₁₅ aroyl" is meant arylcarbonyl, including benzoyl, naphthoyl and anthranoyl.

By the term "C₆-C₁₄ aryl" is meant a mono or polycyclic carbocyclic aromatic radical, including phenyl, naphthyl, anthranyl, and the like.

By the term "C₇-C₁₀ aralkyl" is meant a phenyl substituted C₁-C₃ alkyl chain including benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl and the like.

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The anilide phenyl ring substituents in addition to those above include:

"heteroaryl" being a 5-7 membered aromatic ring containing 0-4 nitrogen atoms and 0-1 oxygen or 0-1 sulfur atoms, which can be 1,2-fused with a benzo ring or another heteroaryl ring as defined above; included in this definition are the following:

pyridyl, furyl, pyrrol, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl, and benzoxazolyl, and the like, which can be further substituted by 1-3 of X, Y and Z as defined herein;

"heteroaroyl" including the above described heteroaryl rings attached to a -C(=O)- group including:

pyridoyl, furoyl, pyrroyl, thienoyl, isothiazoloyl, imidazoloyl, benzimidazoloyl, tetrazoloyl, pyrazinoyl, pyrimidoyl, quinoloyl, isoquinoloyl, benzofuroyl, isobenzofuroyl, benzothienoyl, pyrazoloyl, indoloyl, isoindoloyl, purinoyl, carbazoloyl, isoxazoloyl, thiazoloyl, oxazoloyl, benzthiazoloyl, benzoxazoloyl, and the like, which can be further substituted by 1-3 of X, Y and Z as defined herein;

-CONR²R³, where R² and R³ independently are H, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₄ aryl, all as defined above; and together they can form a 5-7 membered saturated heterocyclic ring containing 1-2 nitrogen atoms, and 0-1 oxygen atoms, e.g. piperidino, piperazino, pyrrolidino, morpholino;

-NHCOR², including acetylamino, isobutyrylamino, n-octanoylamino, 2-adamantanoylamino, 2-pyridylcarbonyl-amino, pivaloylamino, benzoylamino, and the like;

-OCOR², including acetoxy, propionoyloxy, cyclopropanecarboxy, 2-adamantanecarboxy, t-butanecarboxy, 2-pyridocarboxy, and the like;

-NR²(CO)R³, including formylamino, acetylamino, butyrylamino, benzamido, 2-adamantanecarboxamido, benzoylamino, and the like;

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-NR²(CO)NHR³, including ureido, N1-benzylureido, N1-ethylureido, N2-methylureido, and the like;

-NHSO₂R², including phenylsulfonamido, methylsulfonamido, benzylsulfonamido, toluenesulfonamido, trifluoromethanesulfonamido, and the like;

-OR², including methoxy, ethoxy, phenoxy, cyclopropoxy, t-butoxy, and the like;

-NR²R³, including methylamino, ethylamino, dimethylamino, diethylamino, diisopropylamino, pyrrolidino, morpholino, and the like;

-CO²R², including methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, benzoxy carbonyl, 2-adamantoxycarbonyl, and the like.

In addition, C₇-C₁₅ aroyl and C₆-C₁₄ aryl can be substituted by 1-3 X, Y or Z substituents as defined herein.

Preferably the anilide ring is monosubstituted, with one of the above-described substituents where at least two of X, Y or Z are H, or where the anilide phenyl ring is completely unsubstituted.

Any substitutions which result in the formation of compounds containing quaternary nitrogen atoms are not intended to be within the scope of the present invention.

Representative compounds of the present invention include the following:

N-(4-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 325°C(d);

N-(3-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 289-291°C;

N-(2-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 297-299°C;

N-phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 293-295°C;

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N-(4-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
mp. 277-279°C;

5 N-(3-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
mp. 227-228°C;

N-(2-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
mp. 274-276°C;

10 N-phenyl-3-oxo-4-methyl-4-aza-5 α -androst-1-en-17 β -carboxamide,

N-phenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide, mp. 285-287°C;

15 N-phenyl-3-oxo-4-aza-5 α -androst-1-en-17 β -carboxamide,

N-phenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp.
281-283°C;

20 N-phenyl-3-oxo-7 β -methyl-4-aza-5 α -androstane-17 β -carboxamide,

N-phenyl-3-oxo-4,7 β -dimethyl-4-aza-5 α -androstane-17 β -carboxamide,

N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -
carboxamide, mp. 287-289°C;

25 N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
carboxamide, mp. 265-267°C;

30 N-(4-carboxyphenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,
mp. 355-357°C;

N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -
androstane-17 β -carboxamide, mp. 149-150°C;

- 10 -

N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 96-98°;

5 N-(2-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide, mp. 128-129°C;

N-(2-methoxycarboxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide, mp. 115-116°C;

10 N-(4-aminophenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide, mp. 295°C;

15 N-(4-aminophenyl)-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp. 304-307°C(d);

N-4-acetamidophenyl-N-acetyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp. 335-336°C;

20 N-4-acetamidophenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp. 144-147°C;

N-4-acetamidophenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide mp. 335-336°C;

25 N-4-pivalamidophenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp. 296-298°C;

N-4-isobutyramidophenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide, mp. 260-261°C,

30 and also including the corresponding compounds wherein the 4-hydrogen substituent is replaced by a methyl or an ethyl radical, and where a delta-one double bond is present.

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Also included within the scope of this invention are pharmaceutically acceptable salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, which can be used as the dosage form for modifying solubility or hydrolysis characteristics or for use as sustained
5 release or prodrug formulations.

Accordingly, the present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of acne vulgaris, seborrhea, female hirsutism as well as benign prostatic hyperplasia, prostatitis, and prostatic carcinoma by oral
10 or parenteral administration of the novel compounds of the present invention.

The present invention is thus also concerned with providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the
15 present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of benign prostatic hypertrophy can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of
20 tablets, capsules, solutions, or suspensions, or by intravenous or intramuscular injection or by subdermal implantation, i.e., in the male dog. The dosage of the products for an adult human/per day or for a male dog can be varied over a wide range varying from 0.5 to 1,000 mg. The compositions are preferably provided in the form of scored
25 tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from
30 about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. Capsules containing the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate,

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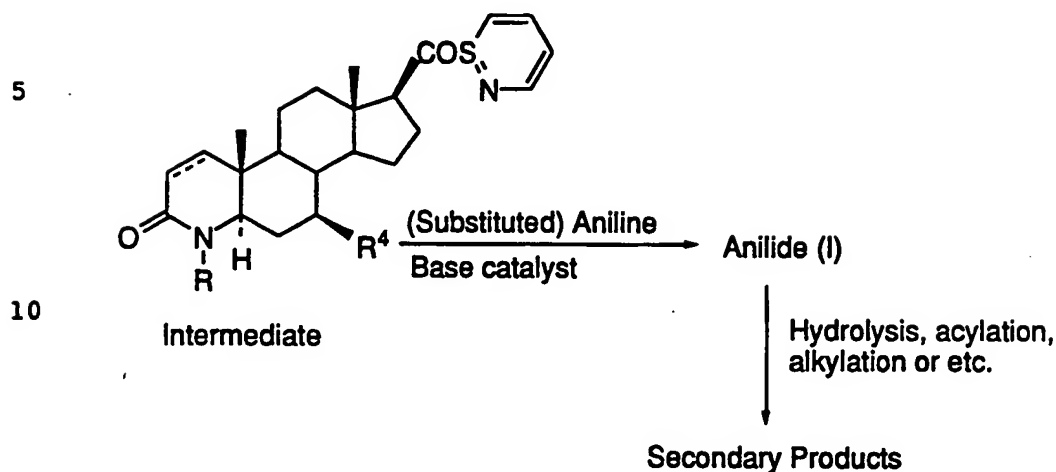
calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corstarch or magnesium stearate. The liquid forms
5 in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methylcellulose and the like. Other dispersing agents which can be employed include glycerin and the like. For parenteral administration, suitably prepared implants or sterile suspensions and solutions are desired. Isotonic
10 preparations which generally contain suitable preservative are employed when intravenous administration is desired.

For the treatment of acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention can be administered in the formula of pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable
15 carrier adapted for topical administration. Parenteral administration is also applicable. These topical pharmaceutical compositions can be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include
20 about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

A method for preparing the novel anilide derivatives of 17 β -carboxy-3-oxo-4-azasteroids of the present invention, already described above in general terms, may be further illustrated by the
25 following examples and synthetic procedure.

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A synthetic procedure for these anilides is:



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As seen in the above diagram, the 2-thiopyridyl intermediate (A, B or C) is reacted with an aniline, or substituted aniline, at room or elevated temperature, e.g. 25-150°C, in the presence of a basic catalyst, e.g. an excess of the starting aniline, for a sufficient time, e.g. 6-24 hours, to form the desired anilide (see Examples 1-3). Conventional workup procedures are utilized to isolate and purify the new anilide.

Further, the new anilide can be subjected to a secondary reaction to yield another new anilide. For example see Examples 4-6. In Example 4, the carboxamido nitrogen is further methylated to form the N-methyl analog. In Example 5, the 4-amino anilide is acylated to yield the 4-isobutyloxyamino-phenyl analog. In Example 6, the 4-carbomethoxy anilide is saponified to the 4-carboxy analog. Thus, by starting with a substituted anilide, containing a functional group X, Y, Z, which can be further modified by a subsequent synthetic reaction, further new anilides can be obtained.

The following are preparations of intermediates useful in the invention and examples of compounds of the invention, which

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should not be construed to be limits on the scope or spirit of the instant invention.

Preparation of Intermediates

5

A. S-2'-pyridyl-3-oxo-4-aza-4-methyl-5 α -androstane-17 β -thiocarboxylate

To a solution of 3-oxo-4-aza-4-methyl-5 α -androstane-17 β -carboxylic acid (7.0g, 21 mmol) in toluene (300 ml) was added aldrithiol (14.7g, 66.7mmol) and triphenylphosphine (16.49g, 62.8 mmol). After stirring the reaction mixture overnight at room temperature, the reaction mixture was concentrated under vacuum and purified by column chromatography over silica gel using 10% acetone/methylene chloride as eluant to give 6.0g of pure product.

10

15 B. S-2'-pyridyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -thiocarboxylate

To a solution of 3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxylic acid (10.0g, 31.5 mmol) in toluene (60 ml) was added aldrithiol (14g, 63.5 mmol) and triphenylphosphine (316g, 61 mmol). After stirring the reaction mixture for overnight at room temperature, the product precipitated out of solution and was filtered (8.4g).

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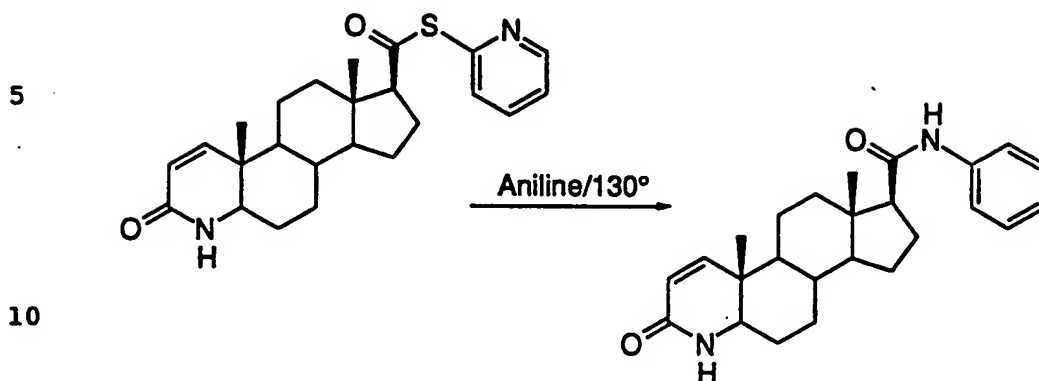
C. S-2'-pyridyl-3-oxo-4-aza-5 α -androstane-17 β -thiocarboxylate

To a solution of 3-oxo-4-aza-5 α -androstane-17 β -carboxylic acid (20.0g, 62.7 mmol) in toluene (120 ml) was added aldrithiol (28g, 127 mmol) and triphenylphosphine (32g, 122 mmol). After stirring the reaction mixture for overnight at room temperature, the product precipitated out of solution and was filtered (20g), Mp 247-249°C.

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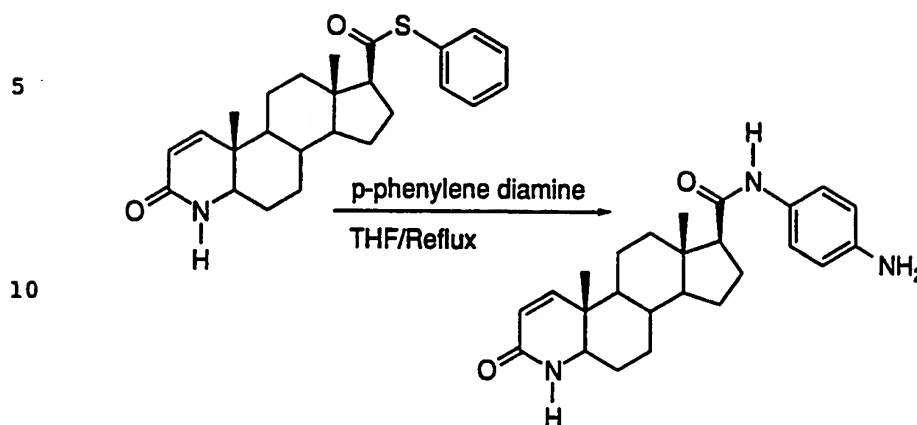
EXAMPLE 1N-phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

15 S-2'-pyridyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
thiocarboxylate (205 mg, 0.5 mmol) was dissolved in aniline (1 ml) and
solution heated at 130° for overnight. The reaction mixture was cooled
and purified by preparative silica gel tlc (30% acetone/methylene
20 chloride) to give pure titled product which was recrystallized from
acetonitrile. Mp 293-295°C. Mass spec. (MS) M⁺ calculated 392.55;
observed 393 (m+1). Anal. calcd for C₂₅H₃₂N₂O₂, C 76.49; H 8.21; N
7.14; Found C 76.59; H 8.26, N 7.13

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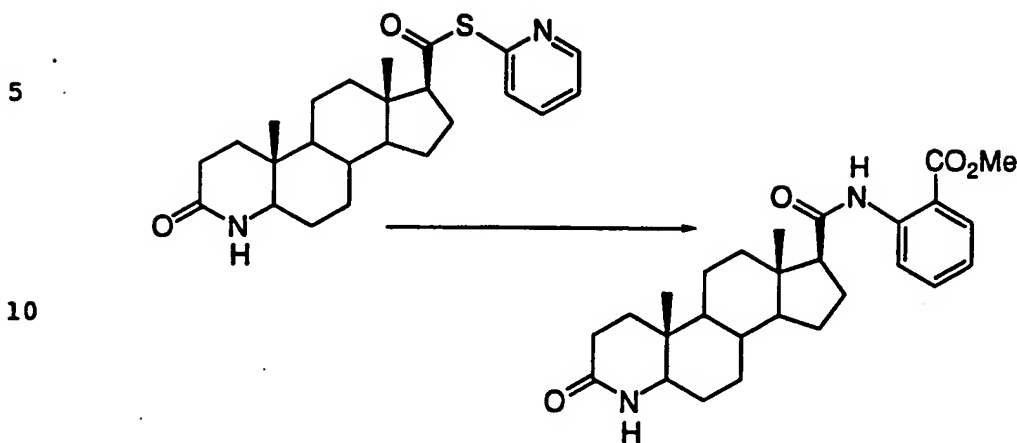
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EXAMPLE 2N-4-aminophenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

S-2'-pyridyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -thiocarboxylate (200 mg) was dissolved in THF (25 ml) and to this p-phenylene diamine (200 mg) was added. After stirring the reaction mixture at reflux temperature for 6 hrs, the reaction mixture was cooled to room temperature and left for overnight. Reaction mixture was concentrated and purified by prep. silica gel tlc. Titled product (140 mg) was recrystallized from hot methanol, Mp 259-262°C. Mass spec. (MS) M⁺ calculated 407.56; observed 408 (m+1). Anal. calcd for C₂₅H₃₃N₃O₂• 0.3 H₂O, C 72.71; H 8.20; N 10.18; Found C 72.89; H 8.01, N 10.27.

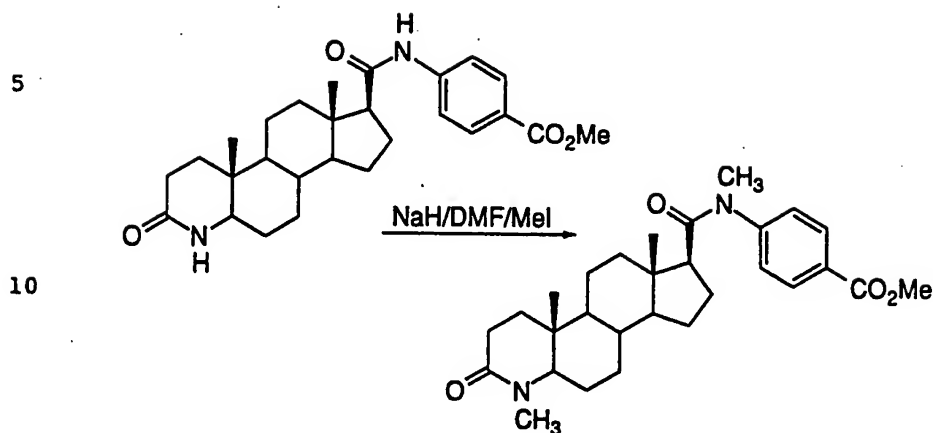
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EXAMPLE 3

15 N-2-carbomethoxyphenyl-3-oxo-4-aza-5α-androstane-17β-carboxamide
S-2'-pyridyl-3-oxo-4-aza-5α-androstane-17β-
thiocarboxylate (207 mg, 0.5 mmol) was dissolved in toluene (4 ml) and
to this 2-methyl anthranilate (199.5 mg, 1.32 mmol) and silver
trifluoromethanesulfonate (129 mg, 0.5 mmol) were added. After
20 stirring the reaction mixture at room temperature for 2 days, the
reaction mixture was concentrated, partitioned between methylene
chloride and water, methylene chloride layer was washed with 5% aq.
NH₄OH, brine, dried, concentrated and purified by prep. silica gel tlc.
Titled product was recrystallized from hot ethylate acetate, Mp 128-
25 129°C. Mass spec. (MS) M⁺ calculated 452.58; observed 452. Anal.
calcd for C₂₇H₃₆N₂O₄• 0.2 H₂O, C 71.08; H 8.04; N 6.14; Found C
71.08; H 8.03, N 5.90.

30

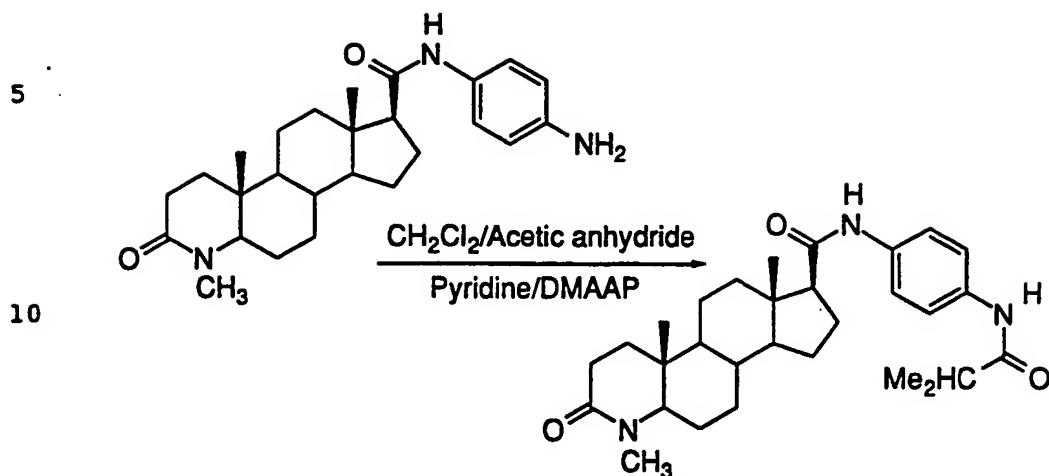
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EXAMPLE 4

N-methyl-N-4-carboxymethylphenyl-3-oxo-4-aza-4-methyl-5 α -androstane-17 β -carboxamide

N-4-carboxymethylphenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxylate (185 mg, 0.41 mmol) was dissolved in 10 ml of DMF and 50 mg of NaH (80% dispersion in mineral oil) was added. After stirring the reaction mixture for 2 hrs at room temperature, 100 micro liter methyl iodide was added. The reaction mixture was stirred further at room temperature for 1 hr, excess of NaH decomposed by careful addition of water, extracted with ethylacetate and organic layer was washed with water, dried and concentrated to give yellow residue. The titled product was purified by column silica gel tlc (30% acetone/CH₂Cl₂), Mp 149-150°C. Mass spec. (MS) M⁺ calculated 480.63; observed 480. Anal. calcd for C₂₉H₄₀N₂O₄• 0.8 H₂O, C 72.47; H 8.39; N 5.83; Found C 70.36; H 8.08, N 5.55.

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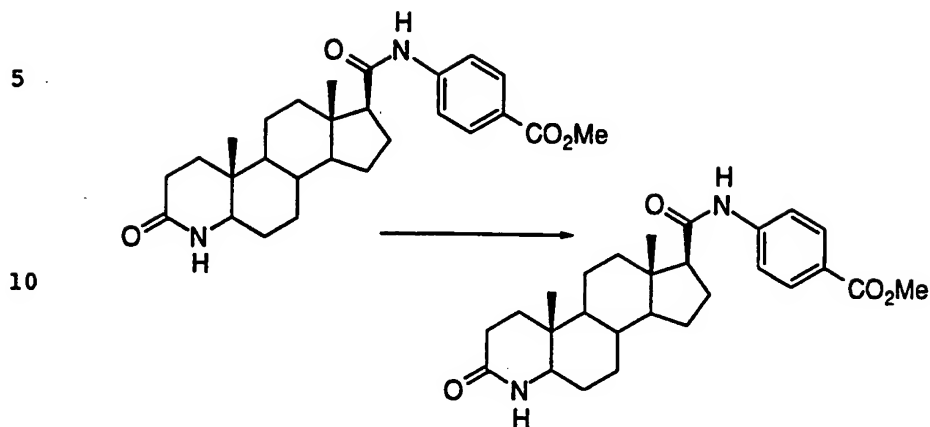
EXAMPLE 5

N-(4-isobutyramidophenyl)-3-oxo-4-methyl-5 α -androstane-17 β -carboxamide

To a solution of N-4-aminophenyl-3-oxo-4-methyl-5 α -androstane-17 β -carboxamide (80 mg, 0.195 mmol) in methylene chloride (10 ml) was added DMAP (71.37 mg, 0.585 mmol), pyridine (157 micro liter) and isobutyric anhydride (161.47 micro liter, 0.975 mmol). After stirring the reaction mixture for 40 min. at room temperature, the reaction mixture was diluted with 30 ml of methylene chloride, washed with aq. NaHCO₃, aq. HCl, water, brine, dried and concentrated. Residue was purified to yield titled product by crystallization from ethyl acetate/methylene chloride, Mp 260-261°C. Mass spec. (MS) M⁺ calculated 493.70; observed 495 (m+2). Anal. calcd for C₃₀H₄₃N₃O₃, C 72.99; H 8.78; N 8.31; Found C 72.96; H 8.70, N 8.34.

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EXAMPLE 6N-(4-carboxyphenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide

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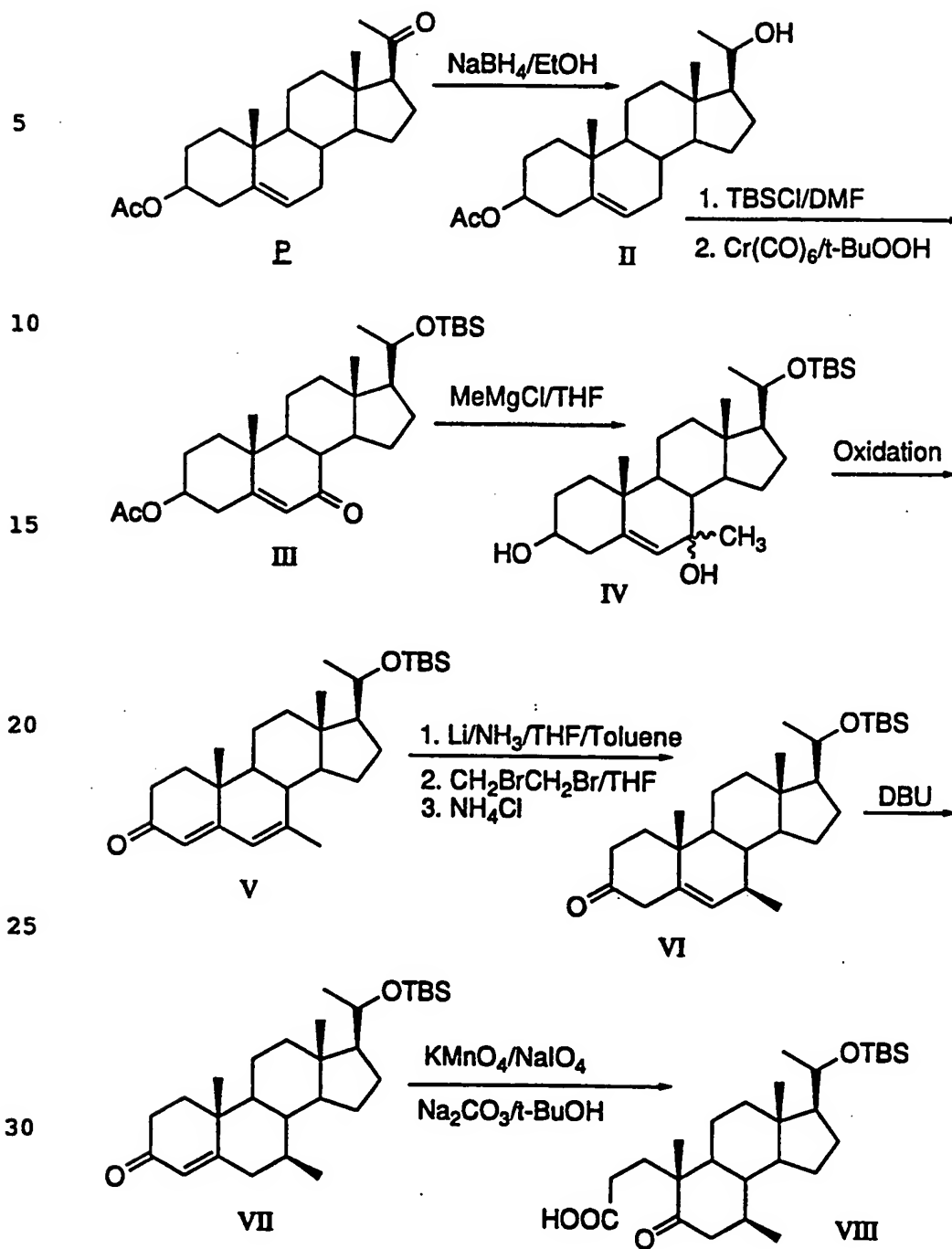
20

N-4-carboxymethylphenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide (100 mg) was dissolved in methanol (10 ml) and 4 ml of 10% aq. KOH was added. After stirring the reaction mixture for 8 hrs at 50°, the reaction mixture was cooled to room temperature, acidified with aq. HCl and methanol removed under vacuum. The solid obtained was filtered and dried to yield titled product, Mp 355-357°C.

25

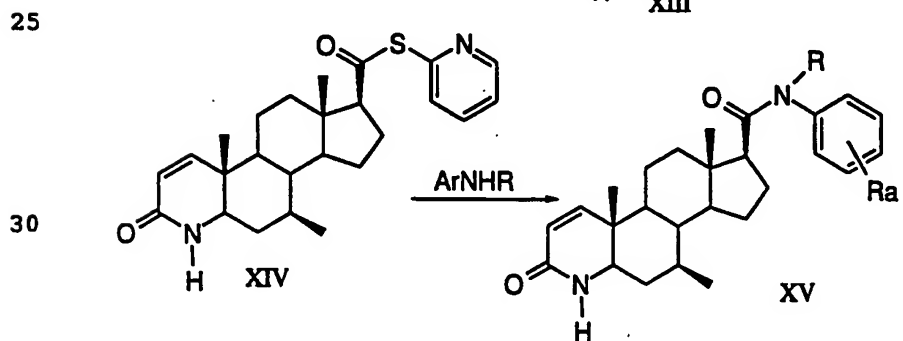
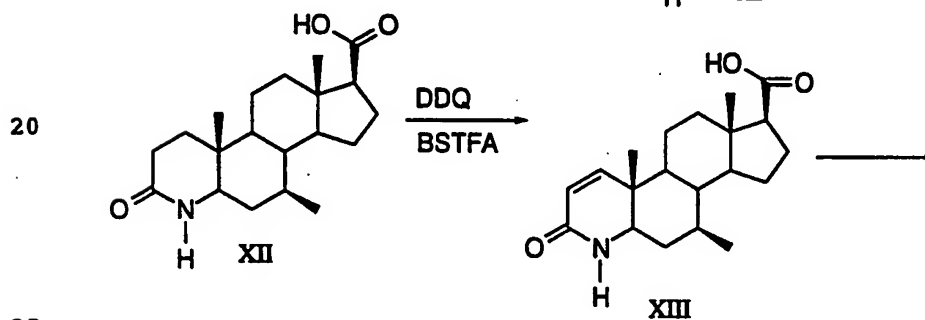
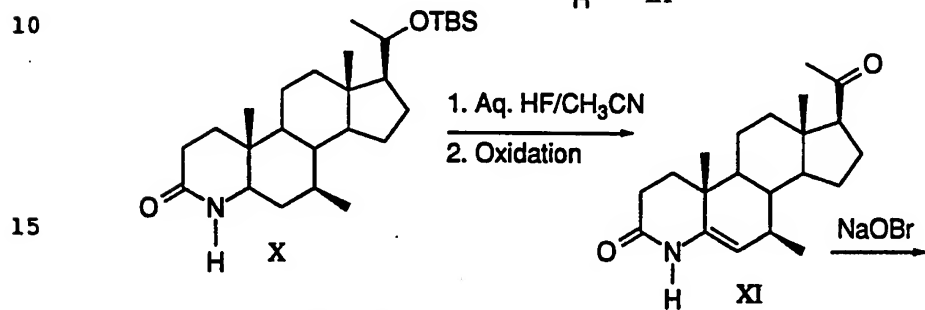
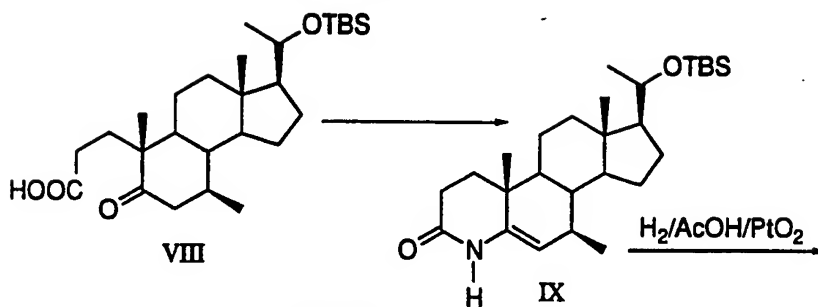
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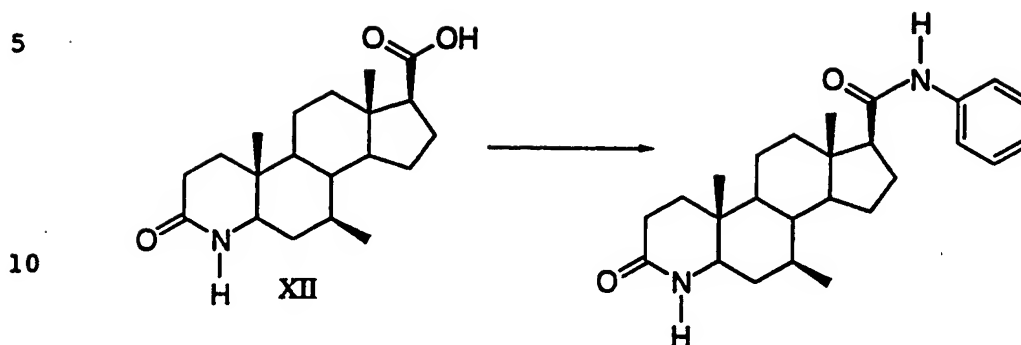
FLWSHEET A

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FLOWSHEET B



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EXAMPLE 77β-Methyl-3-oxo-4-aza-5α-androstane-17β-(N-phenyl)carboxamide

15 The intermediate XII is reacted with aldrithiol/ PPh_3 analogously as described above to give the corresponding 2-thio-pyridylester.

This in turn is reacted with an excess of aniline at elevated temperature, e.g. 100-150°C to yield the above-titled 7β-methyl-azasteroidal anilide.

20

Similarly, using other substituted anilines, other azasteroidal anilides can be produced as described herein.

Preparation of the Starting Material XII

25 As seen in the Flowsheets A and B, pregnenolone-3-acetate P is first reduced to the alcohol II by sodium borohydride in ethanol at -10 to 0°C. The alcohol II is then protected by a dimethyl-t-butyl silyl (TBS) group in DMF with TBS chloride and imidazole as a base at room temperature. The protected alcohol is then oxidized to the

30 corresponding 5-en-7-one III by treatment with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g., acetonitrile, at reflux. The 7-methyl group can be introduced at this point by a Grignard reaction using e.g., methyl magnesium chloride in e.g., anhydrous THF at 0 to -10°C to produce the 7-methyl-7-hydroxy adduct IV. This is

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then oxidized with e.g. aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-methyl-4,6-dien-3-one V. This in turn is reduced via e.g., metal-ammonia, THF and toluene at -78°C to selectively yield the 7-beta-methyl-5-en-3-one VI. In the next step the delta-5 double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0] undec-7-ene) in e.g. refluxing tetrahydrofuran (THF) to produce the 7-methyl-4-ene-3-one, VII. The A ring is next cleaved by treatment with e.g. potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid VIII.

Treatment of the seco-acid with ammonium acetate in glacial acetic acid at 120°C yields e.g., the 7-methyl-4-aza-pregn-5-en-3-one IX. This in turn is selectively reduced with e.g., PtO₂, to remove the 5-double bond to produce the 5 α -hydrogen compound X. The TBS protecting group is next removed by aqueous HF in acetonitrile at room temperature and then oxidized by tetrapropylammonium perruthenate/4-methylmorpholine N-oxide in methylene chloride at room temperature to yield the 17-acetyl compound XI. This is treated with a sodium hypobromite/sodium hydroxide solution in dioxane at 10-15°C to form the starting intermediate 17-carboxylic acid XII, mp. 311-312°C. This is then used as described above to make the 2-thiopyridyl ester and the resulting azasteroidal anilides.

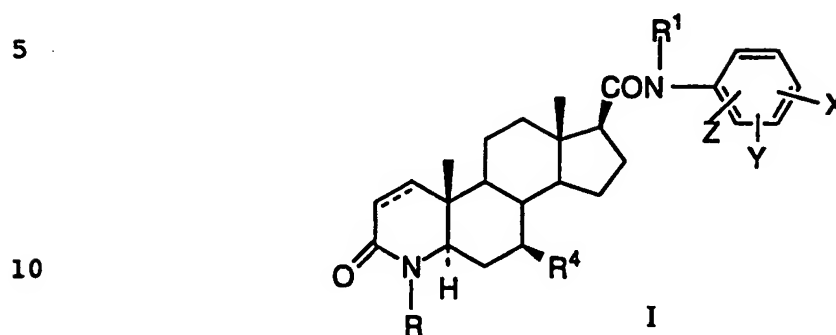
The 1,2-double bond in the A ring can be introduced into XII by DDQ oxidation (see procedure in US Patent 5,084,574) to produce XIII, mp. 328-330°C. Formation of the 2-thiopyridyl intermediate XIV, analogously as described above, and reaction with aniline or substituted anilines as described above produces the corresponding anilides, XV where Ra represents X, Y, Z substituents on the aniline ring.

30

- 25 -

WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein:

R is H, CH₃, or C₂H₅;R¹ is H, C₁-C₁₀ alkyl, or phenyl; andX, Y and Z independently represent -H; -OH; -NH₂; SH; -SC₁-C₄alkyl;-CO₂H; -CN; -C₂-C₁₀ acyl; -C₇-C₁₅ aroyl; straight or branched chainalkyl having 3, 4, 5, 6, 7, or 8 carbon atoms; -C₃-C₈ cycloalkyl; -C₆-C₁₄ aryl; heteroaryl; heteroaroyl; -C₇-C₁₀ aralkyl; -CONR²R³ whereR² and R³ independently are H, C₁-8 alkyl, C₃-8 cycloalkyl, C₆-C₁₄aryl, or R² and R³ together with the nitrogen to which they are attached

form a 5-7 membered saturated heterocyclic ring containing 1-2

nitrogen atoms, and 0-1 oxygen atoms;

-NHCOR²;-OCOR²;-NR²(CO)R³;-NR²(CO)NHR³;-NHSO₂R²;-OR²;-NR²R³;-CO₂R²;

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provided that X, Y, and Z cannot simultaneously be -H when R¹ is -H or C₁-10 alkyl, and provided further that X, Y, and Z cannot simultaneously be -H when R¹ is phenyl and R⁴ is -H or methyl; and

5 wherein the aryl, aroyl, heteroaryl, and heteroaroyl substituents can be unsubstituted or substituted by 1-3 substituents as defined above for X, Y and Z;

R⁴ can be: 1) oxo;
10 2) alpha-hydrogen and beta-hydrogen or a beta-substituent selected from: C₁-C₄ alkyl; C₂-C₄ alkenyl; -CH₂COOH; hydroxy; carboxy; -COOC₁-C₄ alkyl esters; -OCONR⁵R⁶, wherein R⁵ and R⁶ are independently H, C₁-C₄ alkyl, phenyl, benzyl, or R⁵ and R⁶ together with the nitrogen to which
15 they are attached can form a 5-6 membered saturated heterocyclic ring, optionally containing one other heteroatom; -OC₁-C₄ alkyl; -OC₃-C₆ cycloalkyl; -OCOCH₃; halo; hydroxy C₁-C₂ alkyl; halo C₁-C₂ alkyl; trifluoromethyl; and C₃-C₆ cycloalkyl;

3) =CH-R' where R' is H, or C₁-C₄ alkyl;
20 4) spiro:



where R' is H, or C₁-C₄ alkyl;
25 and wherein the dashed line can represent a double bond when present; and pharmaceutically acceptable salts and esters thereof.

2. The compound of Claim 1 wherein at least two of X, Y and Z are hydrogen.

30 3. The compound of Claim 1 selected from the group consisting of:
N-(4-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

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- N-(3-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
N-(2-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
5 phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
N-(4-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
N-(3-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
10 N-(2-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -
carboxamide,
15 N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
carboxamide,
N-(4-carboxyphenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,
20 N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -
androstane-17 β -carboxamide,
N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -
androst-1-ene-17 β -carboxamide,
25 N-(2-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -
carboxamide,
N-(2-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
30 carboxamide,
N-(4-aminophenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,

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N-(4-aminophenyl)-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,

5 N-(4-acetamidophenyl)-N-acetyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,

N-(4-acetamido)phenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,

10 N-(4-acetamidophenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,

N-(4-pivalamido)phenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,

15 N-(4-isobutyramido)phenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,

4. A method for treating the hyperandrogenic conditions of acne, androgenic alopecia, male pattern baldness, female hirsutism, benign prostatic hyperplasia, prostatitis, treatment and/or prevention of
20 prostatic cancer, comprising administering a therapeutically effective amount of the compound of Claim 1 to patients or animals in need of such treatment.

5. A pharmaceutical composition comprising a
25 therapeutically effective amount of the compound of Claim 1 in a pharmaceutically acceptable vehicle.

6. A compound selected from the group consisting of:
N-phenyl-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,
30 N-phenyl-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -carboxamide,
N-phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,
N-phenyl-3-oxo-7 β -methyl-4-aza-5 α -androstane-17 β -carboxamide, and
N-phenyl-3-oxo-4,7 β -dimethyl-4-aza-5 α -androstane-17 β -carboxamide.

AMENDED CLAIMS

[received by the International Bureau on 4 March 1994 (04.03.94);
original claim 3 amended; other claims unchanged (1 page)]

N-(3-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

N-(2-hydroxyphenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

5 N-(4-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

N-(3-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

N-(2-aminophenyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide,

10

N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -
carboxamide,

N-(4-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
15 carboxamide,

N-(4-carboxyphenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,

N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -
20 androstane-17 β -carboxamide,

N-(4-carbomethoxy)phenyl-N-methyl-3-oxo-4-methyl-4-aza-5 α -
androst-1-ene-17 β -carboxamide,

N-(2-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androstane-17 β -
25 carboxamide,

N-(2-carbomethoxy)phenyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -
carboxamide,

30 N-(4-aminophenyl)-3-oxo-4-aza-5 α -androstane-17 β -carboxamide,

N-(4-aminophenyl)-3-oxo-4-methyl-4-aza-5 α -androstane-17 β -
carboxamide,

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US93/09585

A. CLASSIFICATION OF SUBJECT MATTER IPC(5) : C07D 221/02; A61K 31/435, 31/470 US CL : 546/77, 78; 514/284 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 546/77, 78; 514/284 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS Online: Structure Search				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	Jour. Clinical Endoc. and Metab., Vol. 74 No. 2, issued 1992, Diani et al, "Hair Growth Effects of Oral Administration of Finasteride, a Steroid 5 α Reductase Inhibitor, Alone and in combination with Topical Minoxidil in the Balding Stumptail Macaque," pages 345-350. See page 345, para. bridging cols. 102, last 3 lines.	4		
X Y	EP, A, 0,484,094 (Kojima et al) 06 May 1992. See structure I, page 2 and definitions, particularly page 4, lines 7-11.	1, 2, 5 3, 4, 6		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.				
<table border="0"> <tr> <td> * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be part of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family </td> </tr> </table>			* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be part of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be part of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family			
Date of the actual completion of the international search 15 DECEMBER 1993		Date of mailing of the international search report JAN 25 1994		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE		Authorized officer D. DAUS JD <i>[Signature]</i> Telephone No. (703) 308-1235		